

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
18 January 2001 (18.01.2001)

PCT

(10) International Publication Number  
**WO 01/03694 A1**

- (51) International Patent Classification<sup>7</sup>: **A61K 31/343**, A61P 25/00, 25/22
- (74) Common Representative: **H. LUNDBECK A/S**; Att: John Meidahl Petersen, Ottiliavej 9, DK-2500 Valby Copenhagen (DK).
- (21) International Application Number: **PCT/DK00/00377**
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (22) International Filing Date: **7 July 2000 (07.07.2000)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:  
PA 1999 00991      8 July 1999 (08.07.1999)      **DK**
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): **H. LUNDBECK A/S [DK/DK]**; Ottiliavej 9, DK-2500 Valby Copenhagen (DK).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **SANCHEZ, Connie [DK/DK]**; Østerager 58, DK-2600 Glostrup (DK). **HOGG, Sandra [GB/DK]**; Thorvaldsensvej 19, st tv, DK-1871 Frederiksberg (DK).
- Published:  
— *With international search report.*
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



**WO 01/03694 A1**

(54) Title: **TREATMENT OF NEUROTIC DISORDERS**

(57) Abstract: Use of the escitalopram (the S-(+)-enantiomer of citalopram) or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment of neurotic disorders is provided, including anxiety states, in particular generalised anxiety disorder and social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder and panic attacks.

## TREATMENT OF NEUROTIC DISORDERS

### Field of invention

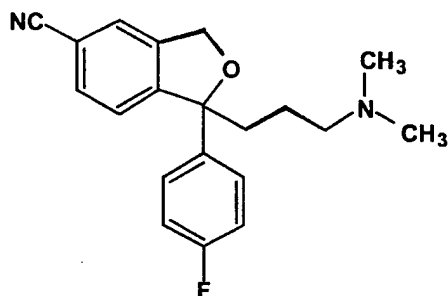
- 5 The present invention relates to the use of the compound escitalopram (INN-name), which is the S-enantiomer of the well-known antidepressant drug citalopram, i.e. (S)-1-[3-(dimethyl-amino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, or a pharmaceutically acceptable salt thereof for the preparation of medicaments for the treatment of neurotic disorders, including anxiety states and panic attacks.

10

### Background of the Invention

Citalopram is a well-known antidepressant drug that has now been on the market for some years and has the following structure:

15



Formula I

- It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, **1982**, *6*, 277-295 and A. Gravem, *Acta Psychiatr. Scand.*, **1987**, *75*, 478-486, and it is now marketed for the treatment of depression and panic disorders. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A 474580.

25

Escitalopram and a method for its preparation are disclosed in US Patent No 4,943,590. The stereo selectivity of citalopram, i.e. the 5-HT-reuptake inhibition in the S-enantiomer, and accordingly, the antidepressant effect of said enantiomer is also disclosed. S-citalopram is now in development as an antidepressant.

30

Studies have shown that patients suffering from neurotic disorders including anxiety disorders, especially generalised anxiety, and panic attacks, in particular in association with agoraphobia, have a quality of life impairment comparable with or greater than the disability found in patients with alcoholism, schizophrenia or personality disorders. Furthermore,  
5 current treatments are not always effective or cause unacceptable side effects.

Consequently, there is a need for alternative therapies useful in the treatment of neurotic disorders.

10 Escitalopram has now been found to show potent effects in models of neurotic disorders such as anxiolytic effect and prominent effect in the treatment of panic attacks and obsessive compulsive disorder.

## 15 **Description of the Invention**

According to the present invention, a novel use of escitalopram, namely for the preparation of a medicament useful in the treatment of neurotic disorders is provided.

20 Throughout this specification and claims the term neurotic disorders is used to designate a group of mental disorders, including anxiety states, in particular generalised anxiety disorder and social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder and panic attacks.

25 The terms generalised anxiety disorder, social anxiety disorder, post traumatic stress disorder and obsessive compulsive disorder are as defined in DSM IV.

The phrase "panic attacks" contemplates treatment of any disease, which is associated with panic attacks including panic disorder, specific phobias, social phobia and agoraphobia in  
30 which panic attacks occur. These disorders are further defined in the DSM IV. A panic attack is a discrete period in which there is a sudden onset of intense apprehension, fearfulness or terror, often associated with feelings of impending doom. During the attack, symptoms such as palpitations, sweating, trembling, sensations of shortness of breath,

feeling of choking, chest pain or discomfort, nausea, feeling dizzy, feelings of unreality, fear of losing control or going crazy, fear of dying, paresthesias and chills or hot flushes are present.

- 5   Panic disorders are characterised by recurrent unexpected panic attacks about which there is a persistent concern. Agoraphobia is anxiety about, or avoidance of, places or situations from which escape might be difficult or in which help may not be available in the event of a panic attack. Specific phobia and social phobia (together formerly simple phobia) are characterised by marked and persistent fear that is excessive or unreasonable, cued by the  
10   presence or anticipation of a specific object or situation (flying, heights, animals, seeing blood etc.) or social performance situations.

The disorders in which panic attacks occur are differentiated from each other by the predictability of the occurrence of the attacks, for example, in panic disorder the attacks are  
15   unpredictable and not associated with any particular event, whereas in specific phobia the attacks are triggered by specific stimuli.

The phrase "treatment of panic disorder" means a reduction in the number or prevention of attacks and/or relief of the severity of the attacks. Similarly, the treatment of generalised  
20   anxiety disorder, social anxiety disorder, post traumatic stress disorder and obsessive compulsive disorder include the treatment or prevention of these diseases, or the relief of the symptoms thereof.

According to the invention, escitalopram may be used as the base of the compound or as a  
25   pharmaceutically acceptable acid addition salt thereof or as an anhydrate or hydrate of such salt. The salts of the compound used in the invention are salts formed with non-toxic organic or inorganic acids, in particular the oxalate.

Escitalopram has been found to show prominent effects different from the effects of the  
30   racemate in the "Inhibition of footshock-induced ultrasonic vocalisation in adult rats" - test, the "Mice Black and White Test" setup, and in the polydipsia test. These models are standard

animal models for anxiolytic effect and effect on panic attacks and for obsessive compulsive disorder, respectively.

According to the invention, escitalopram or a pharmaceutically acceptable salt thereof may  
5 be administered in any suitable way e.g. orally or parenterally, and it may be presented in  
any suitable form for such administration, e.g. in the form of tablets, capsules, powders,  
syrups or solutions or dispersions for injection. Preferably, and in accordance with the  
purpose of the present invention, the compound of the invention is administered in the form  
of a solid pharmaceutical entity, suitably as a tablet or a capsule or in the form of a  
10 suspension, solution or dispersion for injection.

Methods for the preparation of solid pharmaceutical preparations are well known in the art.  
Tablets may thus be prepared by mixing the active ingredients with ordinary adjuvants  
and/or diluents and subsequently compressing the mixture in a convenient tableting  
15 machine. Examples of adjuvants or diluents comprise: corn starch, lactose, talcum,  
magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive  
such as colourings, flavourings, preservatives, etc. may also be used provided that they are  
compatible with the active ingredients.

20 The compound of the invention is most conveniently administered orally in unit dosage  
forms such as tablets or capsules, containing the active ingredient in a dose from about 1.0  
mg to 50 mg, preferably 5 mg/day to 40 mg/day, most preferably 10 mg/day to 20 mg/day.

The oxalate of escitalopram may be prepared as described in US Patent No 4,943,590 and  
25 the base and other pharmaceutically acceptable salts may be obtained therefrom by standard  
procedures.

Thus the acid addition salts used according to the invention may be obtained by treatment of  
escitalopram with the acid in an inert solvent followed by precipitation, isolation and  
30 optionally re-crystallisation by known methods and if desired micronisation of the crystalline  
product by wet or dry milling or another convenient process, or preparation of particles from  
a solvent-emulsification process.

## Pharmacological Tests

Escitalopram was tested in well recognised and reliable test models of effects on neurotic disorders. Citalopram-racemate was included for comparison purposes.

5

### *The footshock- induced vocalisation test in adult rats.*

The footshock- induced vocalisation test in adult rats (described in detail in Sánchez C., Effect of serotonergic drugs on footshock-induced ultrasonic vocalization in adult male rats. *Behav. Pharmacol.* 1993; 4:267-277) is a test for anxiolytic and anti-panic effects.

10

### *Experimental Procedure*

Male rats (Wistar WU, Charles River, Germany), weighing 150-175 g at the beginning of the study were used.

Briefly, test cages (22 cm x 22 cm x 22 cm) made of grey Perspex and equipped with a metal  
15 grid floor were used. Footshocks were delivered from a two pole shocker and a microphone sensitive to ultrasounds in the range of 20-30 kHz was placed in the centre of the lid of the test cage. The ultrasounds were sent from the microphone to a preamplifier and converted from AC signals to DC signals in a signal rectifier. The accumulated time, in which the voltage of the rectified signal was larger than the voltage of a previously determined threshold  
20 level, was recorded.

Twenty-four hours before the first test session the animals were primed. A rat was placed in each test cage and received, immediately thereafter, four 1.0 mA inescapable footshocks each of a duration of 10 sec and with an intershock interval of 5 sec. The animals were left  
25 in the test cage for 6 min after the last shock. On test days, drug or saline was given 30 min before test. The rats received four 1.0 mA inescapable footshocks each of a duration of 10 sec. The intershock interval was 5 sec. Recording of ultrasonic vocalisation started 1 min after the last shock and lasted for 5 min. The total time spent on vocalisation was recorded. After a wash-out period of one week the rats were used in a new test session. The rats were  
30 used for a total of 7-8 weeks. At each test session, the animal groups were randomly allocated to treatment with saline or test drug. Each treatment group consisted of 8 animals,

one saline and 2-4 drug treated groups were included at each session. Each drug was tested at least in two separate experiments with overlapping doses.

### *Results*

- 5 The experiments showed that the maximum effect was 60-70% inhibition for citalopram-racemate whereas escitalopram was able to inhibit vocalisation completely.

### ***Black and White Box Test***

- This is a test for anxiolytic effects. The test model is further described in Sánchez, C. (1995)  
10 Pharmacol. Toxicol. 77, 71-78.

### *Test procedure*

- Male mice (Lundbeck strain, Charles River, Germany) weighing 30-35 g were housed in groups of 4 in macrolon cages type II under a reversed 12 h day /night cycle (lights off 7  
15 p.m.). The mice were adapted to the reversed light/dark cycle for at least 3 weeks prior to testing. The room temperature ( $21 \pm 2^\circ\text{C}$ ), relative humidity ( $55 \pm 5\%$ ), and air exchange (16 times per h) were automatically controlled. The animals had free access to commercial food pellets and water.

- The test box used was designed as described by Sánchez (1995) (*supra*). Briefly, the test box  
20 (45 cm x 27 cm x 27 cm) was open-topped and divided into two compartments (ratio 2:3) by a partition which was black on the side facing the black compartment and white on the side facing the white compartment. The smaller chamber was made of black perspex. The larger chamber was made of white perspex except for the lowest 7.5 cm. This part was made of transparent perspex (outer walls) and black perspex (partition). The white compartment was  
25 connected to the black compartment by a 7.5 cm x 7.5 cm opening in the partition. The floor of the white compartment was divided into 9 fields, and the floor of the black was divided into 6 fields. The white compartment was illuminated by means of a Schott KL 1500 electronic lamp emitting cold light corresponding to a light intensity of 560 Lux. The mouse test-system was fully automated by 2 rows of 11 infrared light sources and photocells in the  
30 transverse direction and 1 row of 16 in the longitudinal direction (lower row). The lower row of photocells (2 cm above cage floor) detected horizontal locomotor activity (crossing, entries, and time in each compartment), whereas the upper row of photocells (5 cm above

cage floor) detected rearing activity. The accumulated data for 1 min intervals were recorded from 4 test boxes simultaneously and stored in a Paradox data base.

The test boxes were placed in a dark and quiet room. The mice were transported to the test room in a darkened container about 2 h before test. The test room was separated into two parts by a black curtain. The drug treatment took place in one part of the room using a minimum of red light. After dosing, the mice were placed individually in macrolon type II cages until test. The pretreatment time was 30 min. The test boxes were placed in the other part of the room. The test was started by placing the mouse in the centre of the brightly-lit white compartment facing the opening to the black compartment. The test duration was 5 min and the number of rears and line crossings between squares in both the black and the white compartment, number of entries into the black compartment and time spent in the white compartment were assessed.

### *Results*

Escitalopram showed prominent effects in this model.

### *Schedule-induced Polydipsia*

Food deprived rats exposed to a procedure in which food is delivered intermittently will drink large amounts of water if given the opportunity to do so. This behavioural phenomenon is called schedule-induced polydipsia and can be considered as an excessive expression of a normal behaviour. Schedule-induced polydipsia is regarded as a model of obsessive-compulsive disorder (Woods et al. 1993).

### *Test Procedure:*

Male wistar rats (Møllegaard) housed in pairs and kept on a food-restricted diet (80% of normal body weight) for 2 weeks before the start of testing and throughout the duration of testing. To induce polydipsia rats were placed in test chambers where a pellet dispenser automatically dispensed one 60 mg food pellet every 60 seconds. Water was available at all times in the test chamber. Rats were tested 4-5 times per week, after 3-4 weeks training 70% of the rats were drinking >10ml per 30 min test session.

Once the rats had attained a steady drinking level compounds could be tested. Citalopram (40 mg/kg) or Lu 26-054 (20 mg/kg) were administered orally 60 min prior to testing and at

10:00 on the non-test days. The water intake was presented as a percentage of the pre-dosing (baseline) level.

*Results:*

- 5 Escitalopram produced a significant reduction in water intake, whereas citalopram was without effect.

All these studies show that escitalopram has potent anti neurotic diseases effects, in particular anxiolytic effects and effects on panic attacks and obsessive compulsive disorder.

**Claims**

1. Use of escitalopram or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment of neurotic disorders.
- 5 2. The use according to Claim 1, **characterised in**, that the medicament is for administration as a unit dose.
3. The use according to Claim 1 or 2, **characterised in**, that the unit dose is containing the  
10 active ingredient in an amount from 1.0 mg to 50 mg, preferably 5 mg/day to 40 mg/day, most preferably 10 mg/day to 20 mg/day.
4. Use of any of Claims 1 to 3, **characterised in**, that the medicament is for the treatment of generalised anxiety disorder.
- 15 5. Use of any of Claims 1 to 3, **characterised in**, that the medicament is for the treatment of social anxiety disorder.
6. Use of any of Claims 1 to 3, **characterised in**, that the medicament is for the treatment  
20 of post traumatic stress disorder.
7. Use of any of Claims 1 to 3, **characterised in**, that the medicament is for the treatment of obsessive compulsive disorder.
- 25 8. Use of any of Claims 1 to 3, **characterised in**, that the medicament is for the treatment of panic attacks.
9. Use of any of Claim 8, **characterised in**, that the medicament is for the treatment of panic disorder.

10. Use of any of Claim 8, **characterised in**, that the medicament is for the treatment of specific phobias.
11. Use of any of Claim 8, **characterised in**, that the medicament is for the treatment of  
5 social phobia.
12. Use of any of Claim 8, **characterised in**, that the medicament is for the treatment of agoraphobia.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00377

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/343, A61P 25/00, A61P 25/22

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, MEDLINE, CAPLUS, EMBASE, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Rev. Contemp. Pharmacother, Volume 10, 1999, A. F. Joubert et al., "Citalopram and Anxiety Disorders" page 79 - page 131 --	1-12
X	ACTA PSYCHIATRICA SCANDINAVICA, Volume 96, 1997, Koponen H. et al., "Citalopram an the treatment of obsessive-compulsive disorder: an open pilot study" page 343 - page 346 --	1-3,7
X	Journal of Serotonin Research, Volume 1, 1996, Dan J. Stein MB et al., "Use of serotonin selective reuptake inhibitor citalopram in obsessive-compulsive disorder" page 29 - page 33 --	1-3,7



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 October 2000

Date of mailing of the international search report

25 -10- 2000

Name and mailing address of the ISA/  
Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM  
Facsimile No. +46 8 666 02 86

Authorized officer

Eva Johansson/GH  
Telephone No. +46 8 782 25 00

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK 00/00377

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J Clin Psychiatry, Volume 59, No 10, October 1998, Ulla M. Lepola et al., "A Controlled, Prospective, 1-Year Trial of Citalopram in the Treatment of Panic Disorder" page 528 - page 534  --	1-3,8-12
P,X	WO 0015220 A1 (ASTRA AKTIEBOLAG), 23 March 2000 (23.03.00)  --	1-12
A	US 4943590 A (KLAUS P. BOEGESOE ET AL), 24 July 1990 (24.07.90), column 2, line 38 - line 40  --	1-12
A	US 5296507 A (TANAKA, Y. ET AL.), 22 March 1994 (22.03.94)  --	1-12
P,A	WO 0034263 A1 (H. LUNDBECK ET AL), 15 June 2000 (15.06.00)  -- -----	1-12

# INTERNATIONAL SEARCH REPORT

Information on patent family members

03/10/00

International application No.

PCT/DK 00/00377

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	0015220	A1	23/03/00	AU	6378299 A	03/04/00
				SE	9803158 D	00/00/00
<hr/>						
US	4943590	A	24/07/90	AT	119896 T	15/04/95
				AU	623144 B	07/05/92
				AU	3629589 A	04/01/90
				CA	1339568 A	02/12/97
				CY	2081 A	16/10/98
				DE	68921672 D,T	27/07/95
				DK	11593 A	01/02/93
				DK	170280 B	24/07/95
				DK	259989 A	15/12/89
				EP	0347066 A,B	20/12/89
				SE	0347066 T3	
				ES	2068891 T	01/05/95
				FI	91527 B,C	31/03/94
				FI	98627 B,C	15/04/97
				FI	892823 A	15/12/89
				FI	941829 A	20/04/94
				FI	20000507 A	06/03/00
				GB	8814057 D	00/00/00
				GR	3015889 T	31/07/95
				HK	139596 A	02/08/96
				HU	211460 B	28/11/95
				HU	9500496 A	28/09/95
				IE	65734 B	15/11/95
				IL	90465 A	24/01/95
				JP	2036177 A	06/02/90
				JP	3038204 B	08/05/00
				JP	3044253 B	22/05/00
				JP	11292867 A	26/10/99
				MX	9203346 A	31/08/92
				NO	172892 B,C	14/06/93
				NO	892447 A	15/12/89
				NZ	229426 A	21/12/90
				PT	90845 A,B	29/12/89
				US	RE34712 E	30/08/94
				ZA	8904476 A	25/04/90
<hr/>						

# INTERNATIONAL SEARCH REPORT

Information on patent family members

03/10/00

International application No.

PCT/DK 00/00377

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
US	5296507	A	22/03/94	AT	112166 T	15/10/94
				AU	644204 B	02/12/93
				AU	8259491 A	12/03/92
				CA	2049368 A	07/03/92
				DE	69104314 D,T	16/02/95
				DK	213290 D	00/00/00
				DK	474580 T	03/04/95
				EP	0474580 A,B	11/03/92
				SE	0474580 T3	
				HK	21595 A	24/02/95
				IE	72160 B	26/03/97
				IL	98968 A	18/06/96
				JP	2109800 C	21/11/96
				JP	4244024 A	01/09/92
				JP	8005787 B	24/01/96
				KR	9702246 B	26/02/97
				NZ	239437 A	24/02/97
				SG	165594 G	12/05/95
				ZA	9106187 A	29/04/92
-----						
WO	0034263	A1	15/06/00	AU	1503600 A	26/06/00
-----						